IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Jo Klaveness et al.
Application No.	:	10/573,606
Filing Date	:	March 28, 2006
Art Unit	:	1618
Title	:	Optical Imaging of Colorectal Cancer
Docket No.	:	PN0368

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REPLY BRIEF

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I. STATUS OF CLAIMS

Claims 13, 15-18, and 20-24 are pending in this application. The Examiner has rejected all of these claims. Appellants are appealing the rejections of Claims 13, 15-18, and 20-24.

II. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues for review in this appeal arise from an Examiner's Answer that was mailed on June 20, 2008.

The Examiner rejects claims 13, 15-18, and 20-24 under 35 U.S.C. § 103(a) as being unpatentable over Marten *et al.* (Gastroenterol., 122, 406-414 (2002) ("Marten") in view of Klaveness *et al.* U.S. Patent No. 6,610,269B1) ("Klaveness") and in further view of Waggoner et al. U.S. Patent No. 6,008,373 ("Waggoner").

The Examiner also rejects claims 13, 15-18,and 20-24 under 35 U.S.C. § 103(a) as being unpatentable over Weissleder *et al.* (Nature Biotech., 1999, 17, 375-378) ("Weissleder") in view of Klaveness and further in view of Waggoner.

III ARGUMENT

Appellants respectfully point out here that they are only addressing the Examiner's Answer ("Answer") dated June 20, 2008 herein. Please see Appellants Appeal Brief dated February 19, 2008 for a complete Responsive Brief.

Appellants respectfully request that The Board of Patent Appeals and Interferences ("Board") should reverse the Examiner's rejection based on the Examiner's Answer for the reasons set forth below.

On page 5 of the Examiner's Response to Appellants, the Examiner refers to Figure 1 of Marten and p. 375 of Weissleder, and argues that the active probe is "a smaller segment of the initial Cy5.5 NIRF probe of 35 kDa".

Appellants refer to Weissleder (p. 375 right hand column), where the nature of the probe is described:

> "We used a synthetic graft copolymer consisting of poly-L-Lysine (PL) sterically protected by multiple methoxypolyethylene glycol (MPEG) side chains....
> Each PL backbone contained an average of 92 MPEG molecules and 11 molecules of Cy5.5 yielding $(Cy5.5)_{11}$-PL-$MPEG_{92}$ (abbreviated as C-PGC). The molecule contains 44 unmodified lysines on the backbone as sites for cleavage by enzymes with lysine-lysine specificity."

The Experimental Section (p.377) of Weissleder makes clear that, whilst the poly-L-lysine part has a molecular weight of 35.5 kDa, 92 MPEG residues each of 5 kDa molecular weight are attached, giving a total average molecular weight for the probe of 480 kDa. That is even before the molecular weight of the 11 Cy5.5 residues is taken into account. Each Cy5.5 dye will have a molecular weight of ca. 1000 Da (Cy5 is 975; Merck Index 14th Edition, entry 2679), so 11 such residues is ca. 11 kDa in total.

Appellants have already drawn attention to the 480 kDa nature of the probe of Weissleder/Marten in their Appeal. That is a matter of fact, clearly discernible from reading the

documents themselves. Consequently, it is highly misleading for the Examiner to imply that the probe of Marten/Weissleder has an "initial" molecular weight of 35 kDa prior to enzyme cleavage. Marten/Weissleder themselves teach very clearly that the probe is of formula $(Cy5.5)_{11}$-PL-$MPEG_{92}$ and that the initial molecular weight of the probe is over 480 kDa. The 35 kDa figure refers only to one element of the probe, the poly-L-lysine (PL) backbone.

Whilst the Examiner is correct that the fragment(s) of Figure 1 of Marten would be of lower molecular weight, Appellants stress that they are fragments of a probe of initial molecular weight 480 -490 kDa (not 35 kDa). That is over an order of magnitude different. Weissleder teaches (see above) that the MPEG side chains sterically protect the lysine side chains. The 35.5 kDa polylysine has ca. 147 lysine residues (molecular weight of lysine = 146). 92 of these are protected with MPEG groups; 11 have a conjugated Cy5.5 dye, leaving ca. 44 unmodified lysine residues.

Figure 1 of Marten is thus, as described therein, a Schematic – it does not show the totality of the polymer. It is important to stress that the initial polylysine has ca. 147 linked lysine residues in total. There are 92 conjugated MPEG groups, each of molecular weight 5 kDa. It is clear that the vast majority of the enzymatically cleaved probes would have multiple MPEG groups. All such fragments having 2 or more MPEG fragments would be outside the scope of the present claims, since the 10 kDa limit of revised Claim 13 would be exceeded.

Additionally, on pages 4 and 5 of the Examiner's Answer, the Examiner characterizes Waggoner as follows:

> "Waggoner teaches that low molecular weight fluorescent probes containing cyanine dyes, linker and proteins have a greater penetration into cellular environments with molecular weights of 500 to 10,000 Daltons".
> [*Emphasis added*]

This characterization is then used to provide the alleged motivation to reduce the molecular weight of the imaging agents of Klaveness and/or Marten and Weissleder.

Appellants refer to their Appeal Brief at pages 8 to 9, where the teaching of Waggoner is analysed. As shown there, Waggoner's use of the team "complex" is crucial – it does not refer to a conjugate with a protein. Consequently, the Examiner's characterization of Waggoner is incorrect. In fact, the Examiner's suggestion that a fluorescent probe including a protein could have a molecular weight in the range 500 to 10,000 Daltons (0.5 to 10 kDa) is nonsense. Many proteins have molecular weights in the region of 100 kDa plus. Even antibody fragments have a molecular weight of ca. 20 to 30 kDa. The alleged teaching of Waggoner contradicts the disclosure of the document itself. The Examiner is improperly applying hindsight and additional teaching to Waggoner, with the error on protein molecular weights providing clear evidence of that fact.

No motivation to use low molecular weight fluorescent probes incorporating proteins of overall molecular weight 500 to 10,000 Dalton exists from Waggoner. The Examiner's motivation to reduce the molecular weight of the imaging agent based on Waggoner simply does not exist within the document itself. The inventive step rejection should therefore be withdrawn.

Accordingly, Appellants respectfully request that the Board should reverse the Examiner's obviousness rejection of claims 13, 15-18, and 20-24.

CONCLUSION

In view of the foregoing, Appellants respectfully request that the Board reverse the rejections of Claims 13, 15-18, and 20-24 as set forth in the Office Action mailed September 24, 2007, that the Board allow the pending claims since they are in condition for allowance, and that the Board grant any other relief as it deems proper.

Dated: August 20, 2008

Respectfully submitted,

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